DOI: https://doi.org/10.3329/medtoday.v35i1.64940

ORIGINAL ARTICLE OPEN ACCESS

Efficacy of Rifaximin in Diarrhoea Predominant Irritable Bowel Syndrome: A Placebo Controlled Clinical Trial

Mohammad Sabidur Rahman *[1], Md. Rezaul Karim [2], Md. Anamul Haque[3]

Abstract

Introduction: *Irritable bowel syndrome is a common chronic functional gastrointestinal disorder characterized by abdominal pain associated with altered bowel habit of either diarrhoea, constipation or both. Its pathogenesis is multifactorial and incompletely understood.The role of gut microbiota in the pathophysiology of IBS is supported by various evidences.These are differences in mucosal and faecal microbiota between patients with IBS and healthy individuals,development of post-infectious IBS and the efficacy of some probiotics and nonsystemic antibiotics such as Rifaximin. Previous study showed resetting microbial diversity via Rifaximin use may lead to a decrease in bacterial fermentation and a reduction in the clinical symptoms of IBS. This study is designed to assess efficacy of Rifaximin in diarrhoea predominant irritable bowel syndrome.* ***Objective:*** *This study was conducted to assess the effectiveness of Rifaximin in diarrhoea predominant irritable bowel syndrome patient.* ***Materials and Methods:*** *This quasi experimental study was conducted on patients aged 18-55 years with IBS-D in department of Gastroenterology, BSMMU during the period of September, 2020 to August, 2021.* ***Results:*** *There was significant improvement on abdominal pain($p < 0.001$), abdominal bloating($p = 0.001$) and satisfaction with bowel movement($p<0.001$) in Rifaximin group at 4th week from baseline and most of which sustained upto 12th week of study. The total IBS-SSS at baseline (328.7 ±13.7) decreased to (231.5±14.2) at 12th week of study in Rifaximin group which was significant ($p < o.oo1$). In placebo group IBS-SSS also gradually decreased from baseline (323.4±17.29) to 12th week (269.3±16.2) but statistically not significant. IBS-QOL score at baseline in Rifaximin group was 64±5.2 and in placebo group was 63.4±5.1. Total IBS-QOL score was increased with time in both Rifaximin and placebo group but none was significant. Conclusion: Rifaximin was more effective than placebo in controlling abdominal pain, abdominal bloating and dissatisfaction with bowel movement after 12th week of study. IBS QOL score was also increased in both groups.*

Keywords: *Irritable bowel syndrome, Rifaximin*

Number of Tables: 07; Number of Figures: 02; Number of References: 17; Number of Correspondences: 02.

***1. Corresponding Author:**
Dr. Mohammad Sabidur Rahman
MBBS, MD(Gastroenterology)
Resident
Department of Gastroenterology
Bangabandhu Sheikh Mujib Medical University Dhaka.
Email:srahmandr22@gmail.com
Mobile: 01715620933

2. Dr. Md. Rezaul Karim
MBBS, MD (Gastroenterology)
Registrar
Chandpur Medical College, Chandpur.

3. Dr. Md. Anamul Haque
Assistant Professor
Department of Gastroenterology
Dhaka National Medical College, Dhaka.

Introduction:

Irritable bowel syndrome is a common chronic functional Gastrointestinal disorder characterized by recurring symptoms of abdominal pain, bloating and altered bowel function in the absence of structural, inflammatory or biochemical abnormalities[1]. Bowel alteration occurs in the form of diarrhoea, constipation or both. IBS is defined according to the Rome IV criteria by recurrent abdominal pain for at least 1 day/week in the last 3 months, which is related to defecation, associated with a change in frequency or form of stools with symptom onset at least 6 months before the diagnosis[8]. Pooled prevalence of IBS worldwide was 11.2% [11]. Its prevalence in Bangladesh is not well known. The overall, unadjusted estimate of IBS was 7.7%. The gender-specific prevalence was 8.6% in women, and 6.7% in men. IBS was 1.36 times more prevalent in females than in males[13]. IBS can be classified according to their predominant symptom. Data from one meta-analysis of community based studies suggest that 22% of sufferer have constipation predominant IBS (IBS-C), 23% diarrhea predominant IBS (IBS-D), 24% mixed (IBS-M) and remainder cannot be classified (IBS-U)[12].The pathogenesis of IBS is still partly understood and composite. There is no known structural lesion for the symptoms. Factors incriminate in IBS pathogenesis including altered gut motility, abnormal intestinal microbiota, low grade inflammation, visceral hypersensitivity, altered pain modulation, 5-Hydroxytryptamine metabolism, CNS dysregulation, psychological and genetic factors[6]. There are non-pharmacological and pharmacological options to treat IBS. Pharmacological treatment of IBS remains elusive as there is no obvious pathophysiological target [14]. Rifaximin is an oral, non-systemic broad spectrum antibiotic. It is poorly absorbed in the digestive tract, which reduces the risk of serious

Received: 26 November 2022 *Accepted revised version:* 23 February 2023

side effects. A number of mechanism of actions have been proposed to account for the clinical efficacy of rifaximin in patients with IBS-D,including a main hypothesis that rifaximin alters the composition of gut microbiota [16]. In addition to the direct antibiotic effects of rifaximin on gut microbiota, rifaximin impacts the function of the gut microbiota (i.e., metabolism,adherence and virulence) [7].

Materials and Methods:

This quasi experimental study was conducted on patients aged 18-55 years with IBS-D in department of Gastroenterology, BSMMU during the period of September, 2020 to August, 2021. Any alternative diagnosis based on clinical history, examination & initial investigations with CBC with ESR, CRP, RBS, TSH, FT4 had been excluded from the study. Study population was divided equally in Rifaximin and placebo group. IBS symptoms were assessed by IBS- QOL and IBS-SSS questionnaire at baseline and during 4th and 12th weeks of study. The collected data were analyzed by computer with help of SPSS version 23. Statistical analysis was done by using appropriate statistical tool like Chi-square test, Students t-test. P< 0.05 was considered significant.

Observation and Result:

A total of 126 patients with IBS-D patient visiting Gastroenterology OPD of BSMMU were enrolled in the study. Among them, 63 patients were allocated in the Rifaximin group, and 63 were in the placebo group. The results are described by the following tables and figures. It was observed that the mean age of the respondents in the rifaximin group were 40.1 ± 8.5(SD) years and in the placebo group were 40.7 ± 8.7(SD) years with more than half of the study population from the age group of 31-50 years (Rifaximin group: 79.4% and placebo group: 76.2%). The majority of the respondents with IBS-D were females in both rifaximin (65.1%) and placebo (60.3%) groups. The difference in age and sex distribution between the two groups were matched (p >0.05).

Table-I: Distribution of demographic factors among the rifaximin and placebo group (n=126)

Variables	Rifaximin Group (n=63) n (%)	Placebo Group(n=63) n (%)	p -value
Age group (years)			
18-20	1 (1.6)	1 (1.6)	
21-30	9 (14.3)	9 (14.3)	0.97*
31-40	18 (28.6)	17 (27)	
41-50	32 (50.8)	31 (49.2)	
51-60	3 (4.8)	5 (7.9)	
Mean age ± SD	40.1 ± 8.5	40.7 ± 8.7	0.66**
Gender			
Male	22 (34.9)	25 (39.7)	0.58*
Female	41 (65.1)	38 (60.3)	

*chi-square test was performed to compare between groups.

**Independent t-test was performed to compare between groups.

IBS-SSS score of the respondents with IBS-D:

The symptom severity score questionnaire consists of 5 questions related to abdominal pain and discomfort, bowel movements and habits and the affects and interference of IBS-D in the respondent's life. Each of the 5 questions generate a maximum score of 100 using prompted visual analogue scales, leading to a total possible score of 500.

Table-II shows the mean total scores of IBS-SSS and IBS-QOL at baseline for rifaximin and placebo groups. There was no significant difference between both groups at the baseline (p > 0.05).

Table-II: Distribution of IBS-SSS and IBS-QOL scores in rifaximin and placebo group at baseline (n=126).

	Rifaximin Group (n=63) Mean ± SD	Placebo Group (n=63) Mean ± SD	p-value*
Total IBS-SSS score	328.7 ± 13.76	323.4 ± 17.29	0.06
Total IBS-QOL score	64 ± 5.2	63.4 ± 5.1	0.62

*Independent t-test was performed to compare between groups.

Table-III: Distribution of IBS-SSS score in rifaximin and placebo group at baseline, 4th week and 12th week

Total IBS-SSS score Mean ±SD	Baseline	4th week	p-value*	12th week	p-value*
Rifaximin group	328.7±13.76	277.7±14.64	<0.001	231.5±14.2	<0.001
Placebo group	323.4±17.29	304.2±10.37	0.31	290.3±16.2	0.21

*p-value between baseline and 4th week, obtained by t test.

**p-value between baseline and 12th week, obtained by t test.

Overall, it was reported that the total IBS-SSS showed improvement in respondents of both the groups, as scores decreased gradually in both groups.Statistical significant improvements were reported in the total IBS-SSS score from baseline to 12th week in rifaximin group. Respondents in placebo group had no significant improvements in their scores from baseline to 4th week and 12th week.

Table-IV: Distribution of clinical improvement in IBS-SSS score among the study participants

IBS-SSS score	4th week n (%)			12th week n (%)		
	Rifaximin group	Placebo group	p-value*	Rifaximin group	Placebo group	p-value*
Decreased by 50 points	35 (61.4)	3 (5.2)	<0.001	53 (96.4)	26 (46.4)	<0.001
Did not decrease by 50 points	22 (38.6)	55 (94.8)		2 (3.6)	30 (53.6)	

*p-value was obtained by chi-square test.

Clinically meaningful improvement in the IBS-SSS scale is defined as a decrease of 50 points in the score. In the current study, it was reported that35 and 53of the study participants showed clinically meaningful improvement in IBS-SSS total score in the rifaximin group at the 4th week of follow-up and 12th week of follow-up visit respectively. In the placebo group, 3 and 26 of the study participants showed improvement at the 4th week and 12th week of follow-up visit respectively. There was a clinically high significant improvement in the IBS-SSS total score in rifaximin group compared to placebo group at 4th week and 12th week of follow-up (p <0.001).

* p-value at 4thweek between rifaximin and placebo group, obtained by independent t-test

**p-value at 12th week between rifaximin and placebo group, obtained by independent t-test

Figure-1: The changes of Total score of IBS-SSS over the baseline,4th week and 12th week in both groups

Overall, it was reported that the total IBS-SSS showed a statistically significant improvement in the rifaximin group in the 4th and 12th week compared to the placebo group (p <0.001) as the severity score decreased gradually in both the groups.

IBS-QOL of Irritable Bowel Syndrome-Diarrhoea:

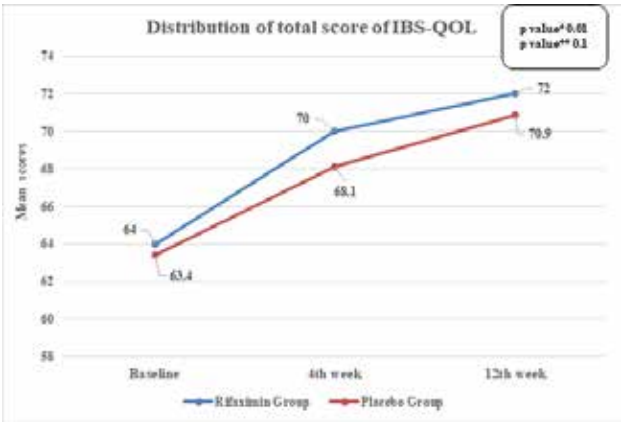
Disease-specific QOL was assessed using the 34-item IBS-QOL questionnaire. This questionnaire consists of eight domains: interference with activities, social reactions, food avoidance, relationships, dysphoria, health worry, sexual health, and body image. All the items are negatively framed with the greatest response scale indicating poorer QOL. As per the IBS-QOL scoring manual, all items were reversed when scored so that as the IBS scores increase, QOL increases as well. All the final raw scores were transformed into a 0 to 100 scale. Using this scale, the lowest possible score (poor QOL) and highest possible score (best QOL) were transformed to 0 and 100, respectively. Raw scores for each subscale were transformed into a scale of 0 to 100 and results were presented as a percentage of the total possible score achieved.

Table-V: Distribution of IBS-QOL scores in rifaximin and placebo group at Baseline, 4th week and 12th week.

Total IBS-QOL score Mean ±SD	Baseline	4th week	p-value*	12th week	p-value*
Rifaximin group	64±5.2	70±4.2	0.04	72 ± 3.43	0.33
Placebo group	63.4 ± 5.1	68.1 ± 3.1	0.45	70.9 ± 3.02	0.69

*p-value between baseline and 4th week, obtained by t-test

**p-value between baseline and 12th week, obtained by t-test



* p-value at 4th week between rifaximin and placebo group, obtained by independent t-test

**p-value at 12th week between rifaximin and placebo group, obtained by independent t-test

Figure-2: The changes of Total score of IBS-QOL over the baseline,4th week and 12th week in both groups.

The overall score of IBS-QOL in both groups showed improvement as the IBS-QOL score increased from baseline to 12th week. However, the improvement inthe 12th week was not statistically significant in the rifaximin group when compared to the placebo group (p>0.05).

Table-VI: Distribution of IBS-QOL score improvements between rifaximin and placebo group.

IBS-QOL score	4th week n (%)			12th week n (%)		
	Rifaximin group	Placebo group	p-value*	Rifaximin group	Placebo group	p-value*
≥10 points	14 (24.6)	10 (17.2)	0.33	27 (49.1)	23 (41.1)	0.4
≥10 points	43 (75.4)	48 (82.8)		28 (50.9)	33 (58.9)	

*p-value was obtained by chi-square test.

Adverse events were observed during the study and were more common in the rifaximin group than the placebo group. However, we did not discontinue the use of rifaximin as the medication didn't lead to any severe harmful outcome. Nausea and headache were the more frequent

adverse events among the respondents of the rifaximin group.

Table-VII: Adverse events between Rifaximin and placebo group (n=126)

Adverse events	Rifaximin Group n=63 n (%)	Placebo Group n=63 n (%)
Nausea	9 (14.5)	3 (4.8)
Anorexia	5 (7.9)	3 (4.8)
Insomnia	3 (4.8)	2 (3.2)
Dry mouth	5 (7.9)	2 (3.2)
Dizziness	4 (6.3)	2 (3.2)
Anxiety	5 (7.9)	2 (3.2)
Tremor	3 (4.8)	2 (3.2)
Headache	10 (15.9)	5 (7.9)

Discussion:

Diarrhea-predominant irritable bowel syndrome (IBS-D) is a common gastrointestinal disorder characterized by recurring abdominal pain, bloating, and loose stools in the absence of structural or biochemical abnormalities[10]. Nonpharmacologic options for the treatment of IBS-D include psychological approaches, dietary and lifestyle modifications, probiotics, and fiber supplementation, although each has shown variable and less than optimal relief of IBS-D symptoms[6,4]. Medical treatment of IBS remains unsatisfactory for many patients and sufferers represent a considerable burden to the health service by consumption of medical consultations and valuable resources [3]. In an attempt to alleviate symptoms, improve quality of life, and reduce expenditure for the condition, several drugs had been sought to evaluate by several clinical researchers. The present study aimed to assess the effectiveness of Rifaximin in diarrhea-predominant IBS patients. Rifaximin is an oral, minimally absorbed, broad-spectrum antimicrobial agent that targets the gastrointestinal tract and is associated with a low risk of clinically relevant bacterial antibiotic resistance[15,7,5,2]. Due to the lack of intestinal absorption, rifaximin has no systemic side effects and is therefore suitable for chronic use. Administration of rifaximin was shown to be effective in the short-term treatment of small intestinal bacterial overgrowth [17], and in managing intestinal gas production and related symptoms in open-label trials involving patients with functional abdominal symptoms and uncomplicated diverticular disease [9]. This study was held among 126 diagnosed patients of IBS-D according to Rome IV criteria, where the population was divided into two groups: Placebo Group and Rifaximin Group and each group included 63 respondents. The placebo group was treated with placebo drugs and the rifaximin group was treated with rifaximin. In the present study, the mean age of the respondents in the rifaximin group was 40.1 ± 8.5(SD) years and in the placebo group was 40.7 ± 8.7(SD) years with more than half of the study population from the age group of 31-50 years (Rifaximin group: 79.4% and placebo group: 76.2%), which was correlated with a previous study where the mean age for individuals in group A (Rifaximin) was 42.6±12.1 yr versus 39.6±10.9 yr for those in group B (Placebo group) [16].

In the current study, there was a female predominance found between the rifaximin group (65.1%) and the placebo group (60.3%). A previous study also reported a majority percentage of females in both groups (52.4% in Rifaximin group and 57.4% in placebo group) [16]. The symptom severity scores of abdominal pain and discomfort, bloating, bowel habit and affect and interference in life significantly decreased in the rifaximin group over the 12 weeks. At baseline before treatment, the scores in the patients in both the groups were high and not significant but as the duration of the treatment increased the mean scores eventually lowered indicating an improvement. A similar scenario was also observed in a study, where 124 patients with IBS-D were randomized to receive a placebo or rifaximin with a phase of three periods. By the end of phase [2], a significant difference in the subjective feeling of symptom relief was noted with 26/63 (41.3%) of patients in the rifaximin group reporting a decrease in the overall severity of symptoms versus 14/61 (22.9%) in the placebo group B(p = 0.03).This symptomatic improvement was also maintained by the end of phase 3 in the rifaximin group (18/63[28.6%] vs 7/61 [11.5%], p = 0.02)[16]. In the present study, the mean scores of patients reporting symptoms of abdominal pain significantly improved at the 4th week, abdominal distension/bloating and satisfaction with bowel movements were significantly improved at the 4th week and 12th week in the rifaximin group. Similarly, AI Sharara et al. reported in their observations, the scores dropped significantly in the rifaximin group after treatment (at the end of phase 2) to a mean of 104.9 ± 11.4 versus 109.8 ± 12.5 for the placebo group (mean 8 7.6 ± 4.72 vs 2.7 ± 1.8). The drop was significantly more pronounced in the rifaximin arm when compared to placebo (p = 0.03). A mild increase was observed in the symptom score at the end of phase 3 (106.4 ± 12.1 vs 111.4 ± 13.2 for the rifaximin and placebo group, respectively) [16]. A previous study by A Rivkin et al. observed the role and efficacy of rifaximin in the treatment of IBS-D. Patients were randomized to 550 mg rifaximin by mouth 3times/day or placebo for 2 weeks and followed for a total of 3 months. The primary efficacy end point, the proportion of patients having adequate relief of global IBS symptoms for at least 2 of the 4 weeks during the primary follow-up period (weeks 3–6), was achieved by 9% more patients randomized to the rifaximin group when compared with placebo (40.7% vs 31.7%,p<0.001). Bloating was also reduced in 10.3% more patients given rifaximin (p<0.001 vs placebo). Looking at the secondary endpoints of these trials, both daily abdominal pain and daily stool consistency scores were significantly improved by rifaximin treatment both over the study period(3–6 wks, p<0.001 for both endpoints) and the 3-month follow-up period (p=0.006 and p<0.001, respectively).

Conclusion:

In the treatment of IBS-D, rifaximin was safe and superior to placebo in controlling IBS symptoms of abdominal pain, bloating, satisfaction of bowel movements. Improvement in IBS-SSS was significant in rifaximin group compared to placebo. The quality of life domains such as the interference with activities, food avoidance and social reaction scores were significantly improved at 4th week in rifaximin group but there was no significant difference in the overall quality of life of the patients between both groups.

Conflict of Interest: None.

References:

1.Brandt, L.J., Chey, W.D., Foxx-Orenstein, A.E., et al. An evidence-based position statement on the management of irritable bowel syndrome. The American journal of gastroenterology. 2009; 104: S1-S35.
https://doi.org/10.1038/ajg.2008.122
PMid:19521341

2. Debbia, E.A., Maioli, E., Roveta, S. & Marchese, et al. Effects of rifaximin on bacterial virulence mechanisms at supra-and sub-inhibitory concentrations. Journal of Chemotherapy. 2008; 20(2): 186-194.
https://doi.org/10.1179/joc.2008.20.2.186
PMid:18467244

3. Ford, A.C., Forman, D., Bailey, A.G., et al. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. Official journal of the American College of Gastroenterology| ACG. 2008; 103(5): 1229-1239.
https://doi.org/10.1111/j.1572-0241.2007.01740.x

4. Ford, A.C., Quigley, E.M.M., Lacy, B.E., et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Official journal of the American College of Gastroenterology| ACG. 2014; 109(10): 1547-1561.
https://doi.org/10.1038/ajg.2014.202

5.Gerard, L., Garey, K.W. & DuPont, H.L. Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. Expert review of anti-infective therapy. 2005; 3(2): 201-211.
https://doi.org/10.1586/14787210.3.2.201
PMid:15918778

6. Holtmann, G.J., Ford, A.C. & Talley, N.J. Pathophysiology of irritable bowel syndrome. The Lancet Gastroenterology and Hepatology. 2016; 1(2): 133-146.
https://doi.org/10.1016/S2468-1253(16)30023-1
PMid:28404070

7. Jiang, Z.D. & DuPont, H.L. Rifaximin: in vitro and in vivo antibacterial activity-a review. Chemotherapy. 2005; 51(Suppl. 1): 67-72.
https://doi.org/10.1159/000081991
PMid:15855749

8. Lacy, Brian E PhD, MD; Lee, Ryan De MD. Irritable Bowel Syndrome. Journal of Clinical Gastroenterology. May 2005; 39 (5): S230-S242.
https://doi.org/10.1097/01.mcg.0000156110.69232.bb
PMid:15798490

9. Latella, G., Pimpo, M., Sottili, S., et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. International journal of colorectal disease. 2003; 18(1): 55-62.
https://doi.org/10.1007/s00384-002-0396-5
PMid:12458383

10. Longstreth, G.F., Thompson, W.G., Chey, W.D., et al. Functional Bowel Disorders. Gastroenterology. 2006; 130(5): 1480-1491.
https://doi.org/10.1053/j.gastro.2005.11.061
PMid:16678561

11. Lovell RM, F.A. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012; 10: 712-21.
https://doi.org/10.1016/j.cgh.2012.02.029
PMid:22426087

12. Lovell, RM., & Ford, A.C. Effect of gender on prevalence of irritable bowel syndrome in the community: Systematic review and meta-analysis. American Journal of Gastroenterology. 2012; 107(7): 991-1000.
https://doi.org/10.1038/ajg.2012.131
PMid:22613905

13. Masud MA, Hasan M, Azad Khan AK. Irritable bowel syndrome in a rural community in Bangladesh. Prevalence, symptom pattern and health seeking behavior. Am J Gastroenterol. 2001;96:1547-52.
https://doi.org/10.1111/j.1572-0241.2001.03760.x
PMid:11374697

14. Miller LE. Study design considerations for irritable bowel syndrome clinical trials. Ann Gastroenterol. 2014;27(4):338-345.

15. Pimentel, M., Lembo, A., Chey, W.D., et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. New England journal of medicine. 2011; 364(1):22-32.
https://doi.org/10.1056/NEJMoa1004409
PMid:21208106

16. Sharara, A.I., Aoun, E., Abdul-Baki, H., et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Official journal of the American College of Gastroenterology| ACG. 2006; 101(2): 326-333.
https://doi.org/10.1111/j.1572-0241.2006.00458.x

17. Stefano, D. Rifaximin versus chlortetracycline in the short term treatment of small intestinal bacterial overgrowth. Alimentary pharmacology & therapeutics. 2000; 14(5): 551-556.
https://doi.org/10.1046/j.1365-2036.2000.00751.x
PMid:10792117